Dear Sir, Madam,

Please find hereunder the contribution of

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to the European Commission's *"Public Consultation in Preparation of a Legal Proposal to Combat Counterfeit Medicines for Human Use; Key Ideas for Better Protection of Patients against the Risk of Counterfeit Medicines"* (11 March 2008)

DSM Anti-Infectives B.V.

DSM Anti-Infectives B.V., a Business Group of the Dutch company DSM, is one of the world's leading manufacturers of antibiotic active pharmaceutical ingredients (APIs) and their intermediates. Our Business Group has eleven wholly- and partly owned manufacturing sites worldwide.
We highly appreciate this opportunity for submitting our contribution to this extremely important European initiative.

Introduction

In its role as a member of the European Chemical Industry Council (CEFIC), DSM Anti-Infectives has since April 1998 played a prominent role within CEFIC's Sector Groups APIC (Active Pharmaceutical Ingredients Committee) and - since 2004 - EFCG (European Fine Chemicals Group) in the fight against API (Active Pharmaceutical Ingredient) counterfeiting.
During the past decade our company has been very actively involved in discussions with health authorities, notably those in the EU and in the USA, on the topic of Counterfeit APIs. In addition we have contributed in many other ways, such as through publications and presentations at international conferences, to an increase in the general awareness of this serious problem.
We are convinced that API counterfeiting forms a very concrete threat that is likely to result in human health catastrophes of large magnitudes. The current "heparin affair" is likely to be just a tip of the iceberg and may well compare with events yet to follow in the future as having been only a minor - though certainly a serious and shocking - event.

Therefore, we are pleased to see that the European Commission is, with a strong sense of urgency, preparing an initiative for developing and implementing legislation aimed at combating pharmaceutical counterfeiting, including counterfeiting activities regarding APIs.

Because DSM Anti-Infectives is involved in the manufacture and marketing of APIs and not in the manufacture or marketing of dosage forms we will restrict our input almost entirely to matters relating to APIs, except when dosage form aspects directly impact upon API matters.

General view on the Public Consultation Document ("PCD")

Though we regard the rough outline of proposals, as included in the PCD, as an important step forward we find the proposed framework insufficient, too vague and containing on balance too few really new concrete elements with regards to APIs.
As is stated in the PCD itself on its page 4:

"Moreover, it is evident that any legislative measure needs to be complemented by appropriate supervision and enforcement. Any legislation can only be fully effective if it is thoroughly enforced by the competent authorities of the Member States."

We completely agree, but with regards to APIs the PCD unfortunately does not transpose this statement into a set of clear and effective measures.

Many Counterfeit APIs originate from manufacture in countries - notably China and India - where the health authorities are working according to much lower standards than then the ones in place in the EU. In addition, oversight over exported APIs and dosage forms by those authorities is completely lacking, implying that standards applied for exported products are often even much lower than for products for their local markets. Therefore, the protection of EU citizens against Counterfeit APIs depends entirely on adequate oversight, enforcement and deterrence to be brought about by the EU's own frameworks.

In conclusion, more will be needed to provide for sufficient protection of EU citizens against the perils of Counterfeit APIs than what the PCD is proposing. In addition it will be necessary to work with definitions that will indeed encompass all APIs that are posing concrete health threats to EU citizens. Therefore, before listing our specific comments on the PCD and before forwarding our key ideas for the adequate protection of patients we would like to herewith first propose appropriate operational definitions.

Definitions

First of all the term "Counterfeit APIs" needs to be defined.
Secondly it needs to be considered if the health issue for patients, which is the key aspect of this matter, is limited to these Counterfeit APIs or whether the problem related to APIs is broader than that.

In 2005 APIC has issued a definition of Counterfeit APIs, directly derived from EFPIA's below definition of Counterfeit Medicines:

Counterfeit medicines are any brand (or generic) medicines and active pharmaceutical ingredients (APIs) that are deliberately and fraudulently mislabeled by unauthorised parties with respect to source and/or composition and/or therapeutic quality.
(EFPIA, June 2005)

The APIC definition of Counterfeit APIs:

Counterfeit APIs are active pharmaceutical ingredients for which source and / or quality are falsely represented on the label, on the Certificate of Analysis or otherwise.
(APIC, August 2005)

With as a very important, directly derived conclusion:
A medicine that contains a counterfeit API is a counterfeit medicine.

It is therefore quite worrying that one can e.g. regularly hear the presumption being made that in the EU not a single case of counterfeited off-patent medicinal products is known until now. When using the appropriate definitions this statement clearly loses its basis.

Moreover, it is important to point out that a class of APIs not covered by these definitions forms an equally dangerous one: the severely, deliberately (GMP- and/or Regulatory-) non-compliant APIs. The new "umbrella" term "Rogue APIs" is proposed to cover both Counterfeit APIs and seriously, deliberately non-compliant APIs:

Rogue APIs are APIs that are counterfeit and/or severely, deliberately non-compliant.

The common denominator for the two sub-types of Rogue APIs lies in what is also the core of the entire issue, namely potential harm to patients caused by unsafe APIs:

- A medicinal product that contains a counterfeit API is a counterfeit medicinal product that may harm or even kill the patient.
- A medicinal product that contains a severely, deliberately non-compliant API is a severely non-compliant medicinal product that may harm or even kill the patient

Note that Counterfeit APIs are normally severely, deliberately non-compliant ones but severely, deliberately non-compliant APIs are not necessarily always counterfeits. This is why we need to take both API types into consideration.

What is yet lacking is a detailed definition of "severly, deliberately non-compliant APIs".
We think the key to this definition should lie in the word "deliberate". In other words: This should apply when there is involvement of one or more parties that may be expected to be fully aware of EU GMP- and regulatory requirements, but who are yet knowingly bringing severely non-compliant APIs into the supply chain for the EU market.

Some Specific Comments on the Public Consultation Document

- On page 2 a paragraph describes the blurred line between counterfeit and substandard APIs. With the above-described set of definitions we propose to resolve this issue by bringing both categories under the same "umbrella definition" of "Rogue APIs".

- On page 6, last item in the box, reference is made to restricting audits to cases of suspicion of non-compliance with GMP and/or GDP. This is, however, exactly the same approach as hitherto propagated through guidance by the EU, regarding the inspections of API manufacturers. We would like to stress once more that non-compliance can only be determined through audits and inspections. Suspicions up front, or the absence of these, have little meaning and should not be used as leading guiding principles.

- On page 13 in the first box the first "key idea" listed is to make auditing of API suppliers mandatory. To our knowledge such audits are already mandatory now, so we think this key idea adds nothing to what is already in force.

- Moreover, the first box on page 13 doesn't contain any item that could be called "appropriate and thorough supervision and enforcement" as called for under point 3 (Legislative Strategy and Impact Assessment) of the PCD.

- The second box divided over pages 13 and 14 only adds one element to the currently existing situation, namely that unannounced inspections may be carried out. This would be a very meager addition to a current, in our view highly inadequate API inspectional approach. And yet again it is stipulated in this box that API inspections shall be carried out "if there is suspected non-compliance". As pointed out above and at previous occasions, non-compliance can only be determined through thorough audits and inspections. Suspicions up front, or the absence of these, have little meaning and should not be used as leading guiding principles. The approach to be used should instead adhere to the principles "appropriate and thorough supervision and enforcement" as called for under point 3 (Legislative Strategy and Impact Assessment) of the PCD.

We support the geographical focus for inspections as worded in the last item in this box, provided that priority setting will be done on a global basis. In other words, manufacturers / traders / brokers / distributors located within the EU and those located outside the EU should together to be subjected to one and the same risk-based priority setting. Inspection priorities should not be based on proximity; they should be based on risk.

Key Ideas for Adequate Protection of Patients against Counterfeit APIs

DSM Anti-Infectives fully support the proposals as forwarded by the EFCG and Aschimfarma in their letters of 17 December 2007 and 16 January 2008, respectively, to the Cabinet of Commissioner Verheugen (Mr. Nils Behrndt) after a meeting between delegates of these two industry associations with Mr. Behrndt, held on 6 December 2007.

We herewith attach copies of the two respective letters to Mr. Behrndt:

Letter to Nils Behrndt Dec 2007.pdf Letter to Nils Behrndt Jan 2008.pdf

However, we would like to emphasize that in our view these letters contain proposals that can be divided into two categories, namely on the one hand a category of “absolute musts” and on the other hand a category of “also important measures”, where the latter should be seen as second priority ones that should not hinder or delay the implementation of any of the “absolute must” items.

The 10 items to be included within the to be developed legislation as “absolute musts” are in our view:

1. Only APIs covered by a GMP Certificate issued by a competent authority in the EU as a result of a successful inspection should be allowed for use in the manufacture of medicinal products destined for the EU market. Such GMP Certificates should be included in the corresponding Marketing Authorisation Applications and, for importation into the EU, should be part of the documentation to be checked by EU customs. These and other proposed requirements of course should also cover APIs imported into the EU as already included within final medicinal products.

2. Worldwide API inspections by European competent authorities should be prioritized through a risk-based system taking into account that also geographical location is an important criterion for determining potential risk. In addition, the involvement of middlemen (brokers, traders) should be a key criterion for assuming strongly increased risk. Involved middlemen should all be subject to inspections with the very highest priority.
We think that only by erecting a central EU unit for coordination of all API inspections to be executed worldwide (a function that could well be added to the current EMEA structure) such a balanced approach may be adequately implemented.

3. API re-inspections should take place on a regular basis (every 2-3 years). Focus on all possibilities of fraud and counterfeiting should be central within the API inspectional approach. The second EFCG / Aschimfarma letter to Mr. Behrndt goes in substantial detail on how to handle these aspects during the various types of inspections.

4. Any problems relating to insufficient resources for worldwide API inspections should be resolved through inspection fees to be charged to the to be inspected companies.

5. Resource problems should also be mitigated by Mutual Recognition Agreements and information exchange with major, reputable authorities from other countries. At this moment in time we would advise very strongly against Mutual Recognition Agreements with countries such as China and India. In our experience the authorities of these countries still have a long way to go before this level of trust may be considered at all.

6. Both the authorities and the industry should have adequate testing methodology in place designed to detect Rogue APIs.

7. A system should be implemented that will allow EU customs to block continued entrance of identified Rogue APIs into the EU. Within this system it should also be possible to block entrance into the EU of all APIs originating from specific manufacturers and/or traders who have a proven record of being intensively involved in the Rogue API business.

8. Measures / sanctions / penalties against all parties involved in manufacturing, trafficking and use of Rogue APIs should be such that the deterrent effect will be extremely strong. All such measures should be made fully public without exception.

9. A licensing system for API traders and brokers must be put into place in order to “separate the chaff from the wheat”. The middlemen section of the supply chain should also be fully drawn into the domain that is regulated by law and should be subject to thorough inspections.

10. As to the liability of the Qualified Persons we would recommend that the EU will carefully assess how this is legally arranged in Switzerland.

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